Drawing Amendments

Figure 25A has been amended to include the oligonucleotide identifiers depicted in Figure 25B.

Attachment: Replacement Sheet

Annotated Marked-Up Drawings

REMARKS

Amendment to the Specification

The status of priority documents disclosed on the first full page of the specification has been updated. No new matter has been added.

Claim Amendments

Claims 1 and 2 are amended herein to include the recitations that the immunostimulatory oligonucleotide compound is at least 6 nucleotides in length, and that the non-natural pyrimidine nucleoside is selected from the group consisting of 5-hydroxycytosine, 5-hydroxymethylcytosine, N4-alkylcytosine, aracytosine and 4-thiouracil. Support for these amendments can be found throughout the specification, in particular at page 13, line 19 and in Claim 5 as originally filed. Claim 3 has been amended herein to delete the phrase "electron withdrawing group" from the claim. Claim 8 has been amended herein to recite that the non-naturally occurring sugar moiety is arabinose and arabinose derivatives. Support for this amendment can be found throughout the specification, in particular at page 13, line 12 and in Figure 25. Claims 6 and 7 have been amend to change the claim from which they depend. Claims 4 and 5 have been canceled herein. New Claims 39-43 have been added herein, support for these new claims can be found in Claim 5 as originally filed. No new matter has been added.

Amendments to the Drawings

According to the Office Action, the notation used to identify each oligonucleotide compound in Figures 25A and 26A is not consistent with those used in Figures 25B and 26B, respectively. Figure 25A has been amended to include the identifiers 131-1, E709 and E710 next to the proper oligonucleotide so that the identification of oligonucleotides is consistent between Figures 25A and 25B. The identification of the oligonucleotides in Figure 26A, specifically 131-1, E647, E653, is consistent with the identification used in Figure 26B.

Rejection of Claims 3-8 Under 35 U.S.C. §112, Second Paragraph

Claims 3-8 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as

the invention. Specifically, Claim 3 recites a dependency to "claim 0" even though no such claim exists in the instant application. Claims 4-8 depend on Claim 3.

Claim 3 has been amended herein to recite a dependency to "Claim 1". Therefore, Claim 3, as amended, meets the requirements of 35 U.S.C. §112, second paragraph. Dependent Claims 4-8 incorporate all of the limitations of Claim 3 and also meet the requirements of 35 U.S.C. §112, second paragraph. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1-8 Under 35 U.S.C. §112, First Paragraph

Claims 1-8 are rejected under 35 U.S.C. §112, first paragraph, because, according to the office action, the specification does not enable any person skilled in the art to which it pertains to make or use the invention commensurate in scope with the claims. Specifically the Office Action states that the oligonucleotide must comprise a minimum of 5 oligonucleotides in length and that the oligonucleotides must follow the three recited motifs.

Applicants have amended Claim 1 to recite that the oligonucleotide is at least 6 nucleotides in length; however, Applicants disagree that in order to be enabling the oligonucleotide must follow the 3 motifs recited in the Office Action. First, the oligonucleotides need not follow the formula 5'-TCGXX-3', since Fig. 2 of Fearon shows other sequences, such as ATCGATT, which induced IFN-γ and IFN-α. Additionally, this motif is inconsistent with the second and third motifs required by the Office Action, specifically that the oligonucleotide contain two purine bases on the 5' side and two pyrimidine bases on the 3' side of the CpG motif, such as 5'-GACGTT-3' and that the oligonucleotide contain the palindromic 'AACGTT' residue. In fact, the art cited by the Examiner, and several examples provided by the Applicants, disclose numerous immunostimulatory oligonucleotides that do not have these motifs. These motifs were developed to try to optimize specific responses to the oligonucleotides, not to make them immunostimulatory. Thus, the three motifs are not required to enable an immunostimulatory oligonucleotide. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1-4 Under 35 U.S.C. §102(b)

Claims 1-4 are rejected under 35 U.S.C. §102(b) as being anticipated by Krieg *et al.* (hereinafter Krieg). According to the Office Action, Krieg teaches an oligonucleotide compound comprising a dinucleotide of formula 5'-pyrimidine-purine-3', wherein the pyrimidine is a non-natural pyrimidine nucleoside and the purine is a natural purine nucleoside.

Applicants' respectfully disagree. Krieg describes the stimulatory effects of synthetic oligonucleotides that contain one or more CpG dinucleotides. As shown in Table 1, any modification of the C in the CpG dinucleotide resulted in the loss of stimulatory activity of the oligonucleotide. Since Krieg does not teach an **immunostimulatory** oligonucleotide compound comprising an immunostimulatory dinucleotide of formula 5'-pyrimidine-purine-3' wherein pyrimidine is a non-natural pyrimidine nucleoside and purine is a natural or non-natural purine nucleoside, Krieg does not anticipate the claimed invention. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1-4 Under 35 U.S.C. §102(b)

Claims 1-4 are rejected under 35 U.S.C. §102(b) as being anticipated by Schwartz *et al.* (hereinafter Schwartz). According to the Office Action, Schwartz teaches an oligonucleotide compound comprising a dinucleotide of formula 5'-pyrimidine-purine-3', wherein the pyrimidine is a non-natural pyrimidine nucleoside and the purine is a natural purine nucleoside.

Schwartz describes an oligonucleotide compound comprising CG dinucleotide in which the C residue is modified by addition to C-5 and/or C-6 of an electron-withdrawing moiety, for example a halogen. Such a compound is termed by Schwartz as a "modified ISS" (see page 10, lines 6-9).

Claim 1, as amended, recites an immunostimulatory oligonucleotide compound, comprising an immunostimulatory dinucleotide of formula 5'-pyrimidine-purine-3', wherein pyrimidine is a non-natural pyrimidine nucleoside selected from the group consisting of 5-hydroxycytosine, 5-hydroxymethylcytosine, N4-alkylcytosine, aracytosine and 4-thiouracil. Therefore, Schwartz does not anticipate Claim 1, as amended. The remaining claims are dependent upon Claim 1 and are also not anticipated by Schwartz. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 1-6 Under 35 U.S.C. §102(b)

Claims 1-6 are rejected under 35 U.S.C. §102(b) as being anticipated by Zuo *et al.* (hereinafter Zuo). According to the Office Action, Zuo teaches an oligonucleotide compound comprising a dinucleotide of formula 5'-pyrimidine-purine-3', wherein the pyrimidine is a non-natural pyrimidine nucleoside and the purine is a natural purine nucleoside.

Applicants' respectfully disagree. Zuo does not deal with immunostimulatory oligonucleotides or their administration. Rather, Zuo describes the products of oxidative attack on 5-methylcytosine residues in DNA and the extent to which the products lead to deamination. Since Zuo does not teach an **immunostimulatory** oligonucleotide compound comprising an immunostimulatory dinucleotide of formula 5'-pyrimidine-purine-3' wherein pyrimidine is a non-natural pyrimidine nucleoside and purine is a natural or non-natural purine nucleoside, Zuo does not anticipate the claimed invention. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 5-8 Under 35 U.S.C. §103(a)

Claims 5-8 are rejected under 35 U.S.C. §103(a) unpatentable over Krieg in view of Bennett *et al.* (hereinafter Bennett).

As described above, Krieg does not disclose the claim invention because Krieg fails to teach or suggest an **immunostimulatory** oligonucleotide compound comprising an immunostimulatory dinucleotide of formula 5'-pyrimidine-purine-3' wherein pyrimidine is a non-natural pyrimidine nucleoside and purine is a natural or non-natural purine nucleoside. Bennett fails to provide that which Krieg lacks. Bennett only describes antisense compounds capable of modulating, preferably inhibiting, expression of human bcl-x and of its isoforms. Bennett does not teach or suggest immunostimulatory oligonucleotides containing the CpG dinucleotide or the administration of such oligonucleotides to affect an immune response. One of ordinary skill in the art would have had no motivation to combine the descriptions in Krieg and Bennett to arrive at the immunostimulatory oligonucleotide compounds of the instant claims. Therefore, the instant claims are nonobvious over Krieg and Bennett. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 5-8 Under 35 U.S.C. §103(a)

Claims 5-8 are rejected under 35 U.S.C. §103(a) as unpatentable over Schwartz in view of Bennett *et al.* (hereinafter Bennett).

As described above, Schwatz does not disclose the claim invention because Schwartz fails to teach or suggest an immunostimulatory oligonucleotide compound, comprising an immunostimulatory dinucleotide of formula 5'-pyrimidine-purine-3', wherein pyrimidine is a non-natural pyrimidine nucleoside selected from the group consisting of 5-hydroxycytosine, 5-hydroxymethylcytosine, N4-alkylcytosine, aracytosine and 4-thiouracil. Bennett fails to provide that which Schwartz lacks. Bennett only describes antisense compounds capable of modulating, preferably inhibiting, expression of human bcl-x and of its isoforms. Bennett does not teach or suggest immunostimulatory oligonucleotides containing the CpG dinucleotide or the administration of such oligonucleotides to affect an immune response. One of ordinary skill in the art would have had no motivation to combine the descriptions in Schwartz and Bennett to arrive at the immunostimulatory oligonucleotide compounds of the instant claims. Therefore, the instant claims are nonobvious over Schwartz and Bennett. Reconsideration and withdrawal of the rejection are respectfully requested.

Rejection of Claims 7-8 Under 35 U.S.C. §103(a)

Claims 7-8 are rejected under 35 U.S.C. §103(a) as unpatentable over Zuo in view of Bennett *et al.* (hereinafter Bennett).

As described above, Zuo does not disclose the claim invention because Zuo fails to teach or suggest an **immunostimulatory** oligonucleotide compound comprising an immunostimulatory dinucleotide of formula 5'-pyrimidine-purine-3' wherein pyrimidine is a non-natural pyrimidine nucleoside and purine is a natural or non-natural purine nucleoside. Bennett fails to provide that which Zuo lacks. Bennett only describes antisense compounds capable of modulating, preferably inhibiting, expression of human bcl-x and of its isoforms. Bennett does not teach or suggest immunostimulatory oligonucleotides containing the CpG dinucleotide or the administration of such oligonucleotides to affect an immune response. One of ordinary skill in the art would have had no motivation to combine the descriptions in Zuo and Bennett to arrive at the immunostimulatory oligonucleotide compounds of the instant claims. Therefore, the instant

claims are nonobvious over Zuo and Bennett. Reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSION

In view of the above response, it is believed that all claims are in condition for allowance, and it is respectfully requested that the application be passed to issue. If the Examiner feels that a telephone conference would expedite prosecution of this case, the Examiner is invited to call the undersigned.

Respectfully submitted,

Dated: October 25 2004

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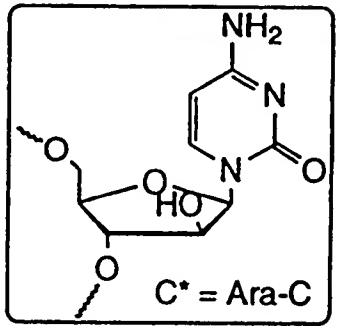
OLIGODEOXYNUCLEOTIDE PHOSPHOROTHIOATES AND SITE OF MODIFICATION

Oligo No.		*Sequence & Modification*	
SEQ ID NO.: 1	1	5'-CTATCTGA<u>CG</u>TTCTCTGT-3'	(131-1)
SEQ ID NO.: 111	2	5'-CTATCTGA<u>C*G</u>TTCTCTGT-3'	(E709)
SEQ ID NO.: 112	3	5'-CTATCTGA<u>CC*</u>TTCTCTGT-3'	(E710)



oligonucleotide identifier added

FIG. 25A